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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,641	11/06/2006	Sandrine Salle	REGIM 3.3-069	8511

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EXAMINER	
WESTERBERG, NISSA M	
ART UNIT	PAPER NUMBER
1618	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,641	SALLE ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4 - 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4 - 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/3/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed May 26, 2009, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 26, 2009 has been entered.

Claim Rejections - 35 USC § 112 – 1st Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. The last two lines of the claim recite the limitation "wherein said first and second skin layers are selected to provide a pH-independent release of said beraprost sodium." The specification provides no description as to how such combinations can be selected and/or any examples of combinations of first and second skin layers that possess this property.

4. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The examiner was unable to find support for the limitation "beraprost sodium composition with high bioavailability and pH sensitivity". If Applicant is in disagreement with the Examiner regarding support for the amended claim, Applicant is respectfully requested to point to page and line number wherein support may be found for the instant invention.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1 and 4 – 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "softening point" does not appear to be a term of art like boiling point or melting point. Therefore the types of material that "soften" at not more than 70°C cannot be determined as soft a material must become at temperatures below this for the limitation to be met cannot de determined.

7. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The preamble of the claim includes the limitation "composition with high bioavailability and pH sensitivity". The term "high bioavailability" in line 2 is a relative term which renders the claim indefinite. The term "high bioavailability" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. While the preamble recites that the composition is pH sensitive, the last two lines of the claim "wherein said first and second skin layers are selected to provide a pH-independent release of said beraprost sodium." It is unclear how these two apparently contradictory limitations can be present in the same claim.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1 and 4 – 8 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al. (JP 02225416) in view of Samejima et al. (US 5,068,112) and Gowan, Jr. et al. (US 5,405,617). This rejection is MAINTAINED for the reasons of record set

forth in the Office Action mailed February 20, 2009 and those set forth below. Note that a complete translation of Hara et al. is included with this Office Action.

Applicant traverses this rejection on the grounds that even if the references are combined they would not result in the claimed invention. Hara and Samejima both teach the addition of a single coating layer to a granule for the purposes of modifying the release of the active pharmaceutical ingredient (API). Gowandoes not cure this deficient as Gowan is directed to taste-masking agents to a formulation either as a single layer coating or as part of a carrier matrix. Again, there is no disclosure as to two different coatings or any disclosure that the coatings may be used in conjunction with sustained or controlled release layers. One skilled in the art would not have been motivated by Gowan to include a layer of an aliphatic or fatty acid ester in conjunction with another sustained release layer. Missing from Gowan is any disclosure on the use of aliphatic or fatty acid esters as coating agents to provide improved bioavailability and sustained or controlled release of an API and in fact teaches that these ingredients "themselves are poorly water soluble or insoluble in water and may inhibit ready release of the coated pharmaceutical actives".

These arguments are unpersuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As none of the references explicitly

discloses two separate layers on the beraprost granule, an anticipation rejection was not made.

Hara et al. discloses that the application of enteric or non-water soluble substance improved the bioavailability of the drug (p 3 ¶ 1; p 4, ¶ 3). The EUDRAGIT® L30D polymer disclosed by Hara et al. is a methacrylic acid/ethyl acrylate copolymer (p 10, ¶ 2), which reads on an acrylic acid/methacrylic acid copolymer. Hara et al. also discloses that the beraprost particles are packed into a capsule (p 9, Application Example 1). Granules are also prepared in which the coating material was ethyl cellulose (p 10, ¶ 4). Samejima is relied upon for the teaching of particle having sizes of not more than 1000 μm, as discussed previously.

The Examiner disagrees with Applicants interpretation of the Gowan reference. The quote provided indicates that the application of the taste mask layer may affect "ready release" of the active ingredient. This argument would be more relevant to art that required immediate release, not the sustained or controlled release products described by Hara et al. and the instant claims. Water soluble additives can be included in this layer if this lack of ready release is undesirable (col 4, ln 64 – 61). The presence of this layer is not criticized, discredited or otherwise discouraged and therefore doe not constitute a teaching away.

Each of these layers serves a function – to control release of the active ingredient and increase the bioavailability (the enteric or non-water soluble layer) and a layer to taste mask the particles (the hot-melt low-melting substance). By preparing a

pharmaceutical product with both layers, a taste-masked pharmaceutical with improved bioavailability is prepared.

Gowan et al. does not need to appreciate that the components can also act to modulate the release of the active, although a case could be made that by teaching that is may inhibit ready release of the active, Gowan indirectly teaches that. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

The combination of the cited prior art discloses beraprost sodium granules that are coated with an first skin layer of a acrylic-acid methacrylic acid copolymer and a second layer of fatty acid ester. Stearyl stearate exemplified by Gowan Jr has a melting point of less than 70°C. The instant claims recite beraprost sodium granules that are coated with a first skin layer of a water-insoluble macromolecular polymer such as acrylic-acid methacrylic acid copolymer and a second layer of a substance having a softening point of not higher than 70°C. The limitations regarding the bioavailability and the pH sensitivity of the composition must be met as both the cited prior art and the instant claims recite beraprost sodium granules that are coated with a first skin layer of a water-insoluble macromolecular polymer such as acrylic-acid methacrylic acid

copolymer and a second layer of a substance having a softening point of not higher than 70°C. The same compositions must necessarily have the same properties.

12. Claims 1 and 4 – 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al. (JP 02225416) in view of Liversidge et al. (US 5,145,684) and Kokubo et al. (JP 01287021; 1989).

Hara et al. discloses that the application of enteric or non-water soluble substance improved the bioavailability of the drug (p 3 ¶ 1; p 4, ¶ 3). The EUDRAGIT® L30D polymer disclosed by Hara et al. is a methacrylic acid/ethyl acrylate copolymer (p 10, ¶ 2), which reads on an acrylic acid/methacrylic acid copolymer. Hara et al. also discloses that the beraprost sodium particles are packed into a capsule (p 9, Application Example 1). Granules are also prepared in which the coating material was ethyl cellulose (p 10, ¶ 4). The size of these particles are greater than 1000 μm as the granules before coating was adjusted to 12 – 16 mesh (p 9, Application Example 1), which for US Std Sieve size, corresponds to sizes ranging from 1190 – 1680 μm.

Hara et al. does not disclose a particle size of less than 1000 μm or the presence of a second skin layer comprised of hot-melt low-melting substance having a softening point of not more than 70°C.

Liversidge et al. discloses that poor bioavailability is a significant problem, particular for drugs that are poorly water soluble (col 1, ln 17 – 21). The rate of dissolution of a particulate drug can increase with increasing surface are, i.e. decreasing particle size (col 1, ln 28 - 29). Particles with an effective average size of

less than 400 nm are set forth to provide high bioavailability of the active ingredients (col 2, ln 38 – 43). Among the drugs whose bioavailability can be increased by this technique are prostaglandins (col 4, ln 2). Beraprost is a prostaglandin.

Kokobu et al. discloses the preparation of wax coating of granules material with paraffin, beeswax, higher alcohols, higher fatty acids, or glycerin fatty acid esters (Abstract ¶ 1), which read on hot-melt low-melting substances having a softening point of not more than 70°C. The wax coating not only masks bitter and other tastes but also solves the problem of untoward granulation for small particles which cannot be entirely avoided using aqueous or organic solvent techniques (Advantage ¶ 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate a wax layer into the granular beraprost sodium particle disclosed by Hara et al. The person of ordinary skill in the art would have been motivated to make those modifications as such a layer not only serves to taste mask but also solves the problem of untoward granulation. The artisan reasonably would have expected success because Kokubo et al. discloses that such wax coatings are suitable for application to pharmaceutical particles. The application of the enteric or non-water soluble coating to the granules results in a pharmaceutical particle that does not exhibit unwarranted granulation, as taught by Kokubo et al., prior to further coating and provides enhanced bioavailability due to the enteric or non-water soluble second polymer coating layer taught by Hara et al.

A smaller particle increases the bioavailability of poorly water soluble drugs like beraprost sodium, as disclosed by Liversidge et al. Therefore one of ordinary skill in the

art would optimize the size of the particle to produce a particle with good availability that was easy to handle and coat in subsequent steps. Optimization of parameters such as particle diameter and the amount of each coating layer is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal diameter and coating thickness in order to best achieve the desired results.

13. Claims 1 and 4 – 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al. (JP 02225416) in view of Liversidge et al. (US 5,145,684) and Araume et al. (JP 59020219)

Hara et al. discloses that the application of enteric or non-water soluble substance improved the bioavailability of the drug (p 3 ¶ 1; p 4, ¶ 3). The EUDRAGIT® L30D polymer disclosed by Hara et al. is a methacrylic acid/ethyl acrylate copolymer (p 10, ¶ 2), which reads on an acrylic acid/methacrylic acid copolymer. Hara et al. also discloses that the beraprost sodium particles are packed into a capsule (p 9, Application Example 1). Granules are also prepared in which the coating material was ethyl cellulose (p 10, ¶ 4). The size of these particles are greater than 1000 μm as the granules before coating was adjusted to 12 – 16 mesh (p 9, Application Example 1), which for US Std Sieve size, corresponds to sizes ranging from 1190 – 1680 μm.

Hara et al. does not disclose a particle size of less than 1000 μm or the presence of a second skin layer comprised of hot-melt low-melting substance having a softening point of not more than 70°C.

Liversidge et al. discloses that poor bioavailability is a significant problem, particular for drugs that are poorly water soluble (col 1, ln 17 – 21). The rate of dissolution of a particulate drug can increase with increasing surface are, i.e. decreasing particle size (col 1, ln 28 - 29). Particles with an effective average size of less than 400 nm are set forth to provide high bioavailability of the active ingredients (col 2, ln 38 – 43). Among the drugs whose bioavailability can be increased by this technique are prostaglandins (col 4, ln 2). Beraprost is a prostaglandin.

Araume et al. discloses enteric coating with an undercoating (second layer) of a higher fatty acid such as stearic acid, which reads on a hot-melt low-melting substance having a softening point of not more than 70°C (CAPLUS abstract). This layer prevented chemical interaction from occurring between the drug containing core and the outer enteric coating material (CAPLUS abstract).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate a wax layer into the granular beraprost sodium particle disclosed by Hara et al. The person of ordinary skill in the art would have been motivated to make those modifications as such a results in stable formulations as no interactions occur between the enteric coating layer and the core containing the pharmaceutical ingredient. The artisan reasonably would have expected success because Araume et al. discloses that such wax coatings are suitable for undercoating of

enteric-coated pharmaceutical particles, resulting in a stable product without interactions between the enteric coating and the core as taught by Araume et al. that provides enhanced bioavailability due to the second polymer coating layer of an enteric or non-water soluble polymer layer as taught by Hara et al.

A smaller particle increases the bioavailability of poorly water soluble drugs like beraprost sodium, as disclosed by Liversidge et al. Therefore one of ordinary skill in the art would optimize the size of the particle to produce a particle with good availability that was easy to handle and coat in subsequent steps. Optimization of parameters such as particle diameter and the amount of each coating layer is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal diameter and coating thickness in order to best achieve the desired results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

NMW